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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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08/704,159

08/28/96

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OPHD-02304

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HM12/0608

EXAMINER

NAVARRO, A

ART UNIT

PAPER NUMBER

1645

DATE MAILED:

06/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

Applicant(s)

Examiner

Group Art Unit

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

- ☒ Responsive to communication(s) filed on 7/15/99
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- ☒ Claim(s) 10-14 + 25-28 is/are pending in the application.
- Of the above claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 10-14 + 25-28 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

- ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
 - ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.
 - ☐ received in Application No. (Series Code/Serial Number) _____
 - ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Attachment(s)

- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Other _____

Office Action Summary

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DETAILED ACTION

Continued Prosecution Application

1. The request filed on April 15, 1999 (Paper Number 15) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/704,159 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's amendment filed on April 15, 1999 (Paper Number 16) has been received and entered. Consequently claims 10-14 and 25-28 are pending in the instant application.

Claim Rejections - 35 USC § 112

2. The rejection of claims 10-14 and 25-28 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view of Applicant's arguments and Declaration.
3. The rejection of claims 10-14 and 25-28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's arguments.

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Claim Rejections - 35 USC § 103

4. The rejection of claims 10-14 and 25-28 under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al* (Eur. J. Biochem. 189: 73-81 (April 1990)) in view of Binz *et al* (J. Biol. Chem. 265: 9153-9158 (June 1990)), Roitt (Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp 173-178 (1988)), LeClerc *et al* (J. Immunol. 144(8): 3174-3182 (Apr 1990), Kleid (Annals NY Acad. Sci. 413: 23-30 (1983)), and Siegel (J. Clin. Microbiol. 26: 2351-2356 (Nov 1988)), is maintained. Additionally the reference applied to claims 13-14 (Ford *et al*, Protein Expression and Purification 2: 95-107 (1991)) is applied to this rejection.

Applicant's are asserting that there is no motivation to make amended claim 10's vaccine by combining Roitt's hypothetical fusion protein with any other reference, since Roitt only hypothesized that its fusion protein may function as a vaccine. Similarly Applicant's argue that there is no explanation why the mere disclosure of Kleid's fusion protein, in which one of the structural proteins (VP₁) of the foot-and-mouth disease virus is ligated to a peptide encoded by the *E. coli* tryptophan operon, motivates combining this reference with any other reference to make amended claim 10's fusion protein in which a non-toxin protein sequence is ligated to at least a portion of *Clostridium botulinum* type B toxin and/or type E toxins. Applicant's further assert and have included a Declaration which show the advantages of fusion proteins which are soluble and neutralizing of amended claim 10. Applicant's arguments have been fully considered but are not found to be fully persuasive.

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Applicant's arguments are not found to be fully persuasive in view of the teachings of Ford *et al.* Ford *et al.* set forth that the majority of GST fusions studied have been soluble, although some fusions may be insoluble. (Page 96). However, Ford *et al.* set forth that while many foreign proteins expressed intracellularly at high levels in *E. coli* and yeasts are produced as insoluble aggregates, often called refractile or inclusion bodies, these aggregates may be solubilized by using chaotropic agents such as guanidine hydrochloride or urea, and then removing the chaotropic agent to permit protein refolding. (See page 101). Applicant's assert that Kleid's fusion protein, in which one of the structural proteins (VP₁) of the foot-and-mouth disease virus is ligated to a peptide encoded by the *E. coli* tryptophan operon, does not motivate combining this reference with any other reference to make amended claim 10's fusion protein in which a non-toxin protein sequence is ligated to at least a portion of *Clostridium botulinum* type B toxin and/or type E toxins. However, Kleid is cited as demonstrating success in producing fusion protein vaccines. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed Cir. 1986). Applicant's further assert that type A toxin is not recited in amended claim 10, and therefore any teaching of the type A toxin is irrelevant. However, Applicant's arguments are not commensurate in scope with Applicant's claim 10, which recites "A vaccine comprising" consequently, the presence of the type A toxin cannot be excluded since it is encompassed within the breadth of the claim reciting "comprising." Applicant's further assert that there is lack of

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motivation in view of Siegel's disclosure that "the human response to two lots of the MDPH product was significantly greater than to the PDC product for the type B component" however, this same reference reports that response to the types A and E were inferior. (See page 2351). Consequently the motivation to include a fusion protein "comprising" these additional toxins would have been desirable to one of skill in the art at the time of the invention.

Furthermore, Applicant's declaration is not commensurate in scope with the claims as recited. Applicant's Declaration reports that fusion proteins of *Clostridium botulinum* type B and/or type E as soluble proteins was unexpected. However, each of the fusion proteins demonstrated contains a poly-histidine tag. Consequently Applicant's Declaration and arguments are not commensurate in scope with the recited claims which recite "fusion protein comprising a non-toxin protein sequence and at least a portion of one or more *Clostridium botulinum* toxins." For reasons of record in Paper Number 12 as well as the above cited reasons this rejection is maintained.

5. The rejection of claims 13-14 under 35 U.S.C. 103(a) as being unpatentable over Thompson *et al* (Eur. J. Biochem. 189: 73-81 (April 1990)) in view of Binz *et al* (J. Biol. Chem. 265: 9153-9158 (June 1990)), Roitt (Essential Immunology, Sixth Edition, Blackwell Scientific Publications, Boston, MA, pp 173-178 (1988)), LeClerc *et al* (J. Immunol. 144(8): 3174-3182 (Apr 1990)), Kleid (Annals NY Acad. Sci. 413: 23-30 (1983)), and Siegel (J. Clin. Microbiol. 26:

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2351-2356 (Nov 1988)), as applied to claims 10-12 above, and further in view of Ford *et al* (Protein Expression and Purification 2: 95-107 (1991)), is withdrawn.

The following new ground of rejection is applied to the claims:

Claim Rejections - 35 USC § 112

6. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is vague and indefinite in the recitation of "substantially" endotoxin-free. One of skill in the art would be unable to determine the metes and bounds of the claimed limitation. For instance, at what level is "substantially" endotoxin free met, 0.1%, 1.0% 10%, etc. Without a clear definition as to the metes and bounds of "substantially" endotoxin free, one of skill in the art would be unable to practice the broadly claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Navarro, whose telephone number is (703) 306-3225. The examiner can be reached on Monday - Thursday from 8:00 AM - 6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Dr. Anthony Caputa can be reached at (703) 308-3995.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1645 by facsimile transmission. Papers should be faxed to Group 1645 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.



Mark Navarro

Patent Examiner

June 7, 1999